Church, Cynthia S.

From: EDD Master Account [edd@dialog.com]
Sent: Thursday, March 15, 2001 3:11 PM
Subject: P326: PR 1/3,AB/ALL ADDR ACCSC

Record - 1

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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09369261 Genuine Article#: 396LR Number of References: 14
Title: Dose-response trend tests for tumorigenesis adjusted for differences in survival and body weight across doses (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT) ; Kodell RL
Corporate Source: Sci Int Inc,13815 Abinger Court/Little Rock//AR/72212 (REPRINT); US FDA,Natl Ctr Toxicol Res,Jefferson//AR/72079
Journal: TOXICOLOGICAL SCIENCES, 2001, V59, N2 (FEB), P219-225
ISSN: 1096-6080 Publication date: 20010200
Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND
Language: English Document Type: ARTICLE
Abstract: A relationship between rodent body weight and tumor incidence for some tissue/organ sites has been demonstrated in many studies. It is not uncommon for a chemical tested for carcinogenicity to also affect body weight due to toxicity and/or food consumption. In such cases, comparisons of tumor incidence may be biased by body weight differences across dose groups. A simple procedure was investigated for reducing this bias. This procedure divides the animals into a few groups on the basis of body weight. Body weight at 12 months was used, before the appearance of a tumor was likely to affect body weight. Statistics for dose-response trend tests are calculated within body weight strata and pooled to obtain an overall dose-response trend test. This procedure is analogous to stratifying animals on the basis of age at the time of removal from a study to account for differences in ages of animals across dose groups that can affect comparisons of tumor incidence. In this paper, differences in survival times of animals were adjusted by the Poly-3 technique used by the National Toxicology Program. This technique does not require the assignment of cause of death. Several examples from rodent chronic bioassays were investigated, where the high dose group had reduced body weights and associated reductions in tumor incidence. When we analyzed the data by body weight strata, some positive dose-response trends for tumor incidence were demonstrated. In one case, the body weight adjusted analysis indicated that a negative dose-response trend in tumor incidence was a real effect in addition to a body weight reduction. These examples indicate that it is important to consider the effects of body weight changes as low as 10%, and perhaps less, as possibly being caused by chemicals in 2-year bioassays for carcinogenesis. The simple procedure of analyzing tumor incidence within body weight strata can reduce the bias introduced by body weight differences across dose groups.

Record - 2

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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09362027 Genuine Article#: 398BH Number of References: 16
Title: Correlation of blood cholinesterase levels with toxicity of sarin in rats (ABSTRACT AVAILABLE)
Author(s): Young JF (REPRINT) ; Gough BJ; Suber RL; Gaylor DW

PM3001180932

Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

Corporate Source: US FDA,Natl Ctr Toxicol Res, Div Biometry & Risk Assessment,3900 NCTR Rd/Jefferson//AR/72079 (REPRINT); US FDA,Natl Ctr Toxicol Res, Div Biometry & Risk Assessment,Jefferson//AR/72079; RJR Nabisco Inc,Bowman Gray Tech Ctr,Winston Salem//NC/
Journal: JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH-PART A, 2001, V62, N3 (FEB), P161-174
ISSN: 1528-7394 Publication date: 20010200
Publisher: TAYLOR & FRANCIS LTD, 11 NEW FETTER LANE, LONDON EC4P 4EE, ENGLAND
Language: English Document Type: ARTICLE
Abstract: The dose-mortality response curve for sarin when administered to pregnant rats is extremely steep. The pregnant animal either died during the treatment or survived with no observable fetal toxicity. Animals that died displayed many symptoms characteristic of anticholinesterase toxicity. The present study was conducted to determine whether the maternal deaths, clinical observations, and/or weight loss could be correlated with baseline blood cholinesterase levels in individual animals. Cholinesterase levels (plasma and erythrocyte) were obtained prior to, during, and following treatment of nonpregnant rats by gavage with 380 mug/kg/d sarin for 10 d. After the first dose, there was a drop in the plasma cholinesterase levels, which then remained low throughout the dosing period. There was a statistically significant correlation between body weight loss and plasma cholinesterase levels of the sarin dosed animals. The surviving animals also had lower plasma cholinesterase levels and lower body weights, both of which recovered on the cessation of dosing. The erythrocyte cholinesterase levels were not different between treated and nontreated rats. Neither plasma or erythrocyte baseline cholinesterase levels nor relative or absolute cholinesterase decline values could be used as predictors of mortality from sarin administration in rats.

Record - 3

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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08963568 Genuine Article#: 349ZZ Number of References: 9
Title: The use of Haber's Law in standard setting and risk assessment (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT)
Corporate Source: US FDA,NATL CTR TOXICOL RES, 3900 NCTR RD/JEFFERSON//AR/72079 (REPRINT)
Journal: TOXICOLOGY, 2000, V149, N1 (AUG 14), P17-19
ISSN: 0300-483X Publication date: 20000814
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND
Language: English Document Type: ARTICLE
Abstract: Haber's Law simply states that the incidence and/or severity of a toxic effect depends on the total exposure, i.e. exposure concentration (c) rate times the duration time (t) of exposure (c x t). This rule, within constraints, is often used in setting exposure guidelines for toxic substances. Establishing reference doses (acceptable daily intakes) for long-term exposures when only the results of short-term studies are available requires the use of an uncertainty (safety) factor. The value of this uncertainty factor often approximates a value comparable to Haber's Law for extrapolation from short-term to long-term exposure durations. As a default procedure, cancer risk estimates are generally based on the average lifetime daily dose which is derived from the total cumulative exposure, i.e. Haber's (c x t). This has been shown both theoretically and empirically to be valid within a factor of 20 for carcinogenesis. This provides some credence for the use of an additional safety factor of 10, in some instances, for exposures of children to carcinogens. Finally, a generalization of

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Haber's Law, exposure concentration raised to a power times exposure duration, is discussed. (C) 2000 Elsevier Science Ireland Ltd. All rights reserved.

Record - 4

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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08609074 Genuine Article#: 307QV Number of References: 16
Title: New issues in cancer risk assessment (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT)
Corporate Source: US FDA,NATL CTR TOXICOL RES, 3900 NCTR RD, HFT-1/JEFFERSON//AR/72079 (REPRINT)
Journal: DRUG METABOLISM REVIEWS, 2000, V32, N2, P187-192
ISSN: 0360-2532 Publication date: 20000000
Publisher: MARCEL DEKKER INC, 270 MADISON AVE, NEW YORK, NY 10016
Language: English Document Type: ARTICLE
Abstract: When a nonlinear dose-response at low doses can be justified, an acceptable daily intake for a carcinogen can be obtained by dividing a benchmark dose, associated with a low incidence of tumors in animals, by uncertainty factors to account for animal-to-human extrapolation, human variability, and risk reduction from a low observed adverse-effect level. This approach can utilize mechanistic information to justify smaller uncertainty factors than typical default values of 10. If a nonlinear dose-response cannot be justified, traditional linear extrapolation from the benchmark dose to zero sometimes gives similar results. This suggests a unified risk-assessment procedure based on uncertainty factors.

The issue of cross-species extrapolation based on the risk relative to background risks, rather than excess risk, is examined. The relative risk approach reduces the estimates of cancer risk in humans based on common rodent tumors, such as the liver in some strains of mice.

Record - 5

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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08422692 Genuine Article#: BP49Z Number of References: 25
Title: Combining uncertainty factors in deriving human exposure levels of noncarcinogenic toxicants (ABSTRACT AVAILABLE)
Author(s): Kodell RL (REPRINT) ; Gaylor DW
Corporate Source: US FDA,NATL CTR TOXICOL RES, DIV BIOMETRY & RISK ASSESSMENT/JEFFERSON//AR/72079 (REPRINT); US FDA,NATL CTR TOXICOL RES, OFF RISK ASSESSMENT POLICY & RES/JEFFERSON//AR/72079
, 1999, V895, P188-195
ISSN: 0077-8923 Publication date: 19990000
Publisher: NEW YORK ACAD SCIENCES, 2 EAST 63RD ST, NEW YORK, NY 10021ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Series: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Language: English Document Type: ARTICLE
Abstract: Acceptable levels of human exposure to noncarcinogenic toxicants in environmental and occupational settings generally are derived by reducing experimental no-observed-adverse-effect levels (NOAELs) or benchmark doses (BDs) by a product of uncertainty factors (Barnes and Dourson, Ref, 1). These factors are presumed to ensure safety by accounting for uncertainty in dose extrapolation, uncertainty in duration extrapolation, differential sensitivity between humans and animals, and differential sensitivity among humans. The common default value for each uncertainty factor is 10. This paper shows how estimates of means and standard deviations of the approximately lognormal distributions of individual uncertainty factors can be used to estimate

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percentiles of the distribution of the product of uncertainty factors, An appropriately selected upper percentile, for example, 95th or 99th, of the distribution of the product can be used as a combined uncertainty factor to replace the conventional product of default factors.

Record - 6

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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08348363 Genuine Article#: 275CK Number of References: 4
Title: Human cancer risk estimates are reduced when based on relative risk for common rodent tumors
Author(s): Gaylor DW (REPRINT) ; Kodell RL; Chen JJ
Corporate Source: US FDA,NATL CTR TOXICOL RES, 3900 NCTR RD/JEFFERSON//AR/72079 (REPRINT)
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1999, V30, N3 (DEC), P 283-284
ISSN: 0273-2300 Publication date: 19991200
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: LETTER

Record - 7

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

08348357 Genuine Article#: 275CK Number of References: 24
Title: An FDA review of sulfamethazine toxicity (ABSTRACT AVAILABLE)
Author(s): Poirier LA (REPRINT) ; Doerge DR; Gaylor DW; Miller MA; Lorentzen RJ; Casciano DA; Kadlubar FF; Schwetz BA
Corporate Source: NATL CTR TOXICOL RES,DIV MOL EPIDEMIOL/JEFFERSON//AR/72079 (REPRINT); NATL CTR TOXICOL RES,DIV BIOCHEM TOXICOL/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,OFF DIRECTOR/JEFFERSON//AR/72079; CTR VET MED,/ROCKVILLE//MD/20855; US FDA,CTR FOOD SAFETY & APPL NUTR/WASHINGTON//DC/20204; NATL CTR TOXICOL RES,DIV GENET & REPROD TOXICOL/JEFFERSON//AR/72079
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1999, V30, N3 (DEC), P 217-222
ISSN: 0273-2300 Publication date: 19991200
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: REVIEW
Abstract: Recently, changes have been proposed in the criteria historically used in the evaluation of the applicability to humans of some of the results obtained from the rodent carcinogenicity bioassay data, These questions center on the suitability of the rodent model for agents that exert their toxic effects via specific enzyme interactions and endocrine mechanisms which appear to be inoperative within humans. Within the U.S. Food and Drug Administration (FDA), this issue has been brought to the forefront of concern with the recent application for a New Animal Drug Application for sulfamethazine (SMZ). A panel of FDA experts from the National Center for Toxicological Research (NCTR), the Center for Veterinary Medicine (CVM), and the Center for Food Safety and Applied Nutrition has reviewed the sum of the scientific evidence available on the toxicology of SMZ. They noted that, in previous feeding studies at NCTR, high doses of SMZ were associated with significant incidences of thyroid tumors in mice and rats. The panel also notes that the tumorigenic activity of SMZ in rodents was due to its goitrogenic activity, resulting in constant stimulation of the thyroid by TSH, Humans, on the other hand, mere found to be insensitive to the SMZ-like inhibition of thyroid function. Further, apart from X-irradiation and radioactive iodine, there are no other physical or chemical agents known to cause thyroid tumors in humans. Thus, the

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expert panel concludes that the best scientific information available indicates that elevated levels of TSH and the consequent thyroid tumors would not be produced under approved use conditions of SMZ. This conclusion is in agreement with recommendations made by three other panels, viz. the World Health Organization, the U.S. Environmental Protection Agency, and CVM, which also evaluated the public health risk of SMZ.

Record - 8

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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08146233 Genuine Article#: 251PY Number of References: 10
Title: Dose-response trend tests for tumorigenesis, adjusted for body weight (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT) ; Kodell RL
Corporate Source: US FDA,NATL CTR TOXICOL RES, 3900 NCTR RD/JEFFERSON//AR/72079 (REPRINT)
Journal: TOXICOLOGICAL SCIENCES, 1999, V49, N2 (JUN), P318-323
ISSN: 1096-6080 Publication date: 19990600
Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND
Language: English Document Type: ARTICLE
Abstract: Several studies have demonstrated a relationship between rodent body weight and tumor incidence for some tissue/organ sites. It is not uncommon for a chemical tested for carcinogenicity to also affect body weight. In such cases, comparisons of tumor incidence may be biased by body-weight differences across dose groups. A simple procedure was investigated for reducing this bias. This procedure divides the animals into a few groups based on body weight. Body weight at 12 months was used, before the appearance of a tumor was likely to affect body weight. Statistics for dose-response trend tests are calculated within body weight strata and pooled to obtain an overall dose-response trend test. This procedure is analogous to that currently used, of stratifying animals, based on their age at the time of removal from a study. Age stratification is used to account for differences in animal age across dose groups, which can affect comparisons of tumor incidence. Several examples were investigated where the high-dose group had reduced body weights and associated reductions in tumor incidence, When the data were analyzed by body-weight strata, some positive dose-response trends for tumor incidence were demonstrated. In one case, the weight-adjusted analysis indicated that a negative dose-response trend in tumor incidence was a real effect, in addition to a body weight reduction. These examples indicate that it is important to consider the effects of body weight changes as low as 10%, and perhaps below, that were caused by chemicals in 2-year bioassays for carcinogenesis. The simple procedure of analyzing tumor incidence within bodyweight strata can reduce the bias introduced by weight differences across dose groups.

Record - 9

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

08102997 Genuine Article#: 226QW Number of References: 0
Title: 677C->T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene may be a maternal risk factor for Down Syndrome.
Author(s): James SJ; Pogribna M; Pogribny IP; Yi P; Gaylor DW
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: FASEB JOURNAL, 1999, V13, N4,1,S (MAR 12), PA223-A223
ISSN: 0892-6638 Publication date: 19990312
Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998

PM3001180936

Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

Language: English Document Type: MEETING ABSTRACT

Record - 10

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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08038800 Genuine Article#: 239PR Number of References: 40
Title: Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome (ABSTRACT AVAILABLE)
Author(s): James SJ (REPRINT) ; Pogribna M; Pogribny IP; Melnyk S; Hine RJ; Gibson JB; Yi P; Tafoya DL; Swenson DH; Wilson VL; Gaylor DW
Corporate Source: US FDA,NATL CTR TOXICOL RES, DIV BIOCHEM TOXICOL, HFT 140, 3900 NCTR RD/JEFFERSON//AR/72029 (REPRINT); UNIV ARKANSAS MED SCI,DEPT BIOCHEM & MOL BIOL/LITTLE ROCK//AR/72205; UNIV ARKANSAS MED SCI,DEPT NUTR & DIETET/LITTLE ROCK//AR/72205; ARKANSAS CHILDRENS HOSP,DIV PEDIAT GENET/LITTLE ROCK//AR/72202; TRISOMY 21 RES INC,/SAN JOSE//CA/95192; SAGINAW VALLEY STATE UNIV,/UNIV CTR//MI/48710; LOUISIANA STATE UNIV,INST ENVIRONM STUDIES/BATON ROUGE//LA/70803; LOUISIANA STATE UNIV,INST MUTAGENESIS/BATON ROUGE//LA/70803
Journal: AMERICAN JOURNAL OF CLINICAL NUTRITION, 1999, V70, N4 (OCT), P 495-501
ISSN: 0002-9165 Publication date: 19991000
Publisher: AMER SOC CLINICAL NUTRITION, 9650 ROCKVILLE PIKE, SUBSCRIPTIONS, RM L-3300, BETHESDA, MD 20814-3998
Language: English Document Type: ARTICLE
Abstract: Background: Down syndrome, or trisomy 21, is a complex genetic disease resulting from the presence of 3 copies of chromosome 21. The origin of the extra chromosome is maternal in 95% of cases and is due to the failure of normal chromosomal segregation during meiosis. Although advanced maternal age is a major risk factor for trisomy 21, most children with Down syndrome are born to mothers <30 y of age.

Objective: On the basis of evidence that abnormal folate and methyl metabolism can lead to DNA hypomethylation and abnormal chromosomal segregation, we hypothesized that the C-to-T substitution at nucleotide 677 (677C --> T) mutation of the methylenetetrahydrofolate reductase (MTHFR) gene may be a risk factor for maternal meiotic nondisjunction and Down syndrome in young mothers.

Design: The frequency of the MTHFR 677C --> T mutation was evaluated in 57 mothers of children with Down syndrome and in 50 age-matched control mothers. Ratios of plasma homocysteine to methionine and lymphocyte methotrexate cytotoxicity were measured as indicators of functional folate status.

Results: A significant increase in plasma homocysteine concentrations and lymphocyte methotrexate cytotoxicity was observed in the mothers of children with Down syndrome, consistent with abnormal folate and methyl metabolism Mothers with the 677C --> T mutation had a 2.6-fold higher risk of having a child with Down syndrome than did mothers without the T substitution (odds ratio: 2.6; 95% CI: 1.2, 5.8; $P < 0.03$).

Conclusion: The results of this initial study indicate that folate metabolism is abnormal in mothers of children with Down syndrome and that this may be explained, in part, by a mutation in the MTHFR gene.

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07827911 Genuine Article#: 212UX Number of References: 20
Title: A unified approach to risk characterization
Author(s): Gaylor DW (REPRINT) ; Kodell RL; Chen JJ; Krewski D
Corporate Source: US FDA,NATL CTR TOXICOL RES, DEPT HLTH & HUMAN SERV, 3900 NCTR DR/JEFFERSON//AR/72079 (REPRINT); UNIV OTTAWA,FAC MED/OTTAWA/ON/CANADA/
Journal: INHALATION TOXICOLOGY, 1999, V11, N6-7 (JUN-JUL), P575-578
ISSN: 0895-8378 Publication date: 19990600
Publisher: TAYLOR & FRANCIS INC, 325 CHESTNUT ST, SUITE 800, PHILADELPHIA, PA 19106
Language: English Document Type: ARTICLE

Record - 12

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07736092 Genuine Article#: 203FC Number of References: 75
Title: A unified approach to risk assessment for cancer and noncancer endpoints based on benchmark doses and uncertainty safety factors (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT) ; Kodell RL; Chen JJ; Krewski D
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079 (REPRINT) ; UNIV OTTAWA,FAC MED/OTTAWA/ON/CANADA/
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1999, V29, N2,1 (APR), P 151-157
ISSN: 0273-2300 Publication date: 19990400
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE
Abstract: A fundamental goal of toxicology is to determine safe levels of human exposure to toxic substances. In the absence of information to establish dose-response relationships at low exposure levels generally experienced by humans, high-dose to low-dose linear extrapolation is generally used for estimating carcinogenic risks and the no-observed-adverse-effect-level divided by uncertainty (safety) factors is widely used for establishing human exposure guidelines for noncancer effects. The basis and impact of this dichotomy is examined and questioned. It is proposed that a unified approach be adopted for establishing human exposure guidelines for both cancer and noncancer endpoints. It is suggested that a lower confidence limit on the dose estimated to produce an excess incidence of adverse health effects in 10% of the individuals in a human study or 10% of the animals in laboratory experiments be used as a point-of-departure. This dose would be divided by appropriate uncertainty factors to establish human exposure guidelines. For severe irreversible adverse health effects we suggest a total default uncertainty factor (divisor) for animal data on the order of 10,000, which is comparable to current guidelines. For reversible biological effects a smaller default uncertainty factor on the order of 1000 may be employed. This is comparable to the divisor often used currently when the point-of-departure is the lowest-observed-adverse-effect-level. It is asserted that the toxicological information generally available does not warrant numerical estimates of risk at low levels of human exposure. Rather, we support a unified approach for all adverse health effects of dividing a benchmark dose by appropriate uncertainty factors to establish guidelines for human exposures to toxic substances. (C) 1999 Academic Press.

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07673179 Genuine Article#: 194WE Number of References: 26

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Title: Using short-term tests to predict carcinogenic activity in the long-term bioassay (ABSTRACT AVAILABLE)
Author(s): Kodell RL (REPRINT) ; Chen JJ; Jackson CD; Gaylor DW
Corporate Source: US FDA,DIV BIOMETRY & RISK ASSESSMENT, NATL CTR TOXICOL RES, 3900 NCTR RD/JEFFERSON//AR/72079 (REPRINT); US FDA,OFF RISK ASSESSMENT POLICY & RES, NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: HUMAN AND ECOLOGICAL RISK ASSESSMENT, 1999, V5, N2 (APR), P427-443
ISSN: 1080-7039 Publication date: 19990400
Publisher: CRC PRESS INC, 2000 CORPORATE BLVD NW, JOURNALS CUSTOMER SERVICE, BOCA RATON, FL 33431
Language: English Document Type: ARTICLE
Abstract: A method for classifying chemicals with respect to carcinogenic potential based on short-term test results is presented. The method utilizes the logistic regression model to translate results from short-term toxicity assays into predictions of the likelihood that a chemical will be carcinogenic if tested in a long-term bioassay. The proposed method differs from previous approaches in two ways. First, statistical confidence limits on probabilities of cancer rather than central estimates of those probabilities are used for classification. Second, the method does not classify all chemicals in a data base with respect to carcinogenic potential. Instead, it identifies chemicals with highest and lowest likelihood of testing positive for carcinogenicity in the bioassay. A subset of chemicals with intermediate likelihood of being positive remains unclassified, and will require further testing, perhaps in a long-term bioassay. Two data bases of binary short-term and long-term test results from the literature are used to illustrate and evaluate the proposed procedure. A cross-validation analysis of one of the data sets suggests that, for a sufficiently rich data base of chemicals, the development of a robust predictive system to replace the bioassay for some unknown chemicals is a realistic goal.

Record - 14

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07481554 Genuine Article#: 171GA Number of References: 15
Title: Regulatory cancer risk assessment based an a quick estimate of a benchmark dose derived from the maximum tolerated dose (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT) ; Gold LS
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079 (REPRINT) ; LAWRENCE BERKELEY LAB,/BERKELEY//CA/94720; UNIV CALIF BERKELEY,/BERKELEY//CA/94720
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1998, V28, N3 (DEC), P 222-225
ISSN: 0273-2300 Publication date: 19981200
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE
Abstract: The proposed U.S. Environmental Protection Agency carcinogen risk assessment guidelines employ a benchmark dose as a point of departure (POD) for low-dose risk assessment. If information on the carcinogenic mode of action for a chemical supports a nonlinear dose-response curve below the POD, a margin-of-exposure ratio between the POD and anticipated human exposure would be considered. The POD would be divided by uncertainty (safety) factors to arrive at a reference dose that is likely to produce no, or at most negligible, cancer risk for humans. If nonlinearity below the POD is not supported by sufficient evidence, then linear extrapolation from the incidence at the POD to zero would be used for low-dose cancer risk estimation. The carcinogen guidelines suggest that the lower 95% confidence limit on the dose estimated to produce an excess of tumors in 10% of the animals (LTD10) be used for the POD. Due to the relatively narrow range of doses in

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2-year rodent bioassays and the limited range of statistically significant tumor incidence rates, the estimate of the LTD10 obtained from 2-year bioassays is constrained to a relatively narrow range of values. Because of this constraint, a simple, quick, and relatively precise determination of the LTD10 can be obtained by the maximum tolerated dose (MTD) divided by 7. All that is needed is a 90-day study to establish the MTD. It is shown that the LTD10 determined by this relatively easy procedure is generally within a factor of 10 of the LTD10 that would be estimated using tumor incidence rates from 2-year bioassays. Estimates of cancer potency from replicated 2-year bioassays, and hence estimates of cancer risk, have been show to vary by a factor of 4 around a median value. Thus, there may be little gain in precision of cancer risk estimates derived from a a-year bioassay, compared to the estimate based on the MTD from a 90-day study. If the anticipated human exposure were estimated to be small relative to the MTD/7 = LTD10, there may be little value in conducting a chronic 2-year study in rodents because the estimate of cancer risk would be low regardless of the results of a 2-year bioassay. Linear extrapolation to a risk of less than 1 in 100,000 and use of an uncertainty factor, e.g., of 10,000, would give the same regulatory "safe dose." Linear extrapolation to a virtually safe dose associated with a cancer risk estimate of less than one in a million mould be 10 times lower than the reference dose based on the LTD10/10,000.

Record - 15

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07451614 Genuine Article#: 167EV Number of References: 0
Title: Recent bioassay results on coal tars and benzo(a)pyrene: Implications for risk assessment
Author(s): Gaylor DW; Moolgavkar S; Krewski D; Goldstein LS (REPRINT)
Corporate Source: ELECT POWER RES INST,3412 HILLVIEW AVE/PALO ALTO//CA/94304 (REPRINT); ELECT POWER RES INST,/PALO ALTO//CA/94304; US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079; FRED HUTCHINSON CANC RES CTR,/SEATTLE//WA/98104; UNIV OTTAWA,FAC MED/OTTAWA/ON K1H 8M5/CANADA/
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1998, V28, N2 (OCT), P 178-179
ISSN: 0273-2300 Publication date: 19981000
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: EDITORIAL MATERIAL

Record - 16

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

07426555 Genuine Article#: 164KE Number of References: 19
Title: Biologically-based dose-response model for neurotoxicity risk assessment (ABSTRACT AVAILABLE)
Author(s): Slikker W (REPRINT) ; Scallet AC; Gaylor DW
Corporate Source: US FDA,NATL CTR TOXICOL RES, DIV NEUROTOXICOL, 3900 NCTR RD/JEFFERSON//AR/72079 (REPRINT)
Journal: TOXICOLOGY LETTERS, 1998, V103 (DEC 28), P429-433
ISSN: 0378-4274 Publication date: 19981228
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND
Language: English Document Type: ARTICLE
Abstract: Domoic acid is a tricarboxylic amino acid that is structurally-related to kainic acid and glutamic acid. It is produced by phytoplankton that may contaminate seafood. To determine domoate's toxicological effects and their pathogenesis, cynomolgus monkeys were dosed intravenously at one of a range of bolus doses from 0.25 to 4.0

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mg/kg. Histochemical staining, using silver methods, revealed degenerating axons and cell bodies. Doses in the range of 0.5-1.0 mg/kg produced a small area of silver grains restricted to axons of the hippocampal CA2 stratum lucidum, the most sensitive brain area identified. Quantitation of the abundance of these silver grains yielded continuous dose-response data. A four step quantitative risk estimation approach was used: (1) determination of a dose-response model; (2) determination of the distribution of measurements (variability) about the model; (3) determination of an adverse or abnormal level with the use of the control data; and (4) estimation of the probability that a measure is beyond the abnormal level as a function of dose. The currently used safety-factor (S-F) approach, the benchmark (BM) approach and this quantitative (Q) approach was used to assess the same data set. Assuming a 5% oral absorption of domoic acid, acceptable doses would be achieved if subjects ate 200 g of seafood containing 12, 6 and 10 ppm domoic acid for the S-F, BM and Q approaches, respectively. This quantitative approach uses all the available data, takes into account the variability of the data and provides an actual risk at a given dose of domoic acid. (C) 1998 Elsevier Science Ireland Ltd. All rights reserved.

Record - 17

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

07365461 Genuine Article#: 156NT Number of References: 22
Title: Tumors and DNA adducts in mice exposed to benzo[a]pyrene and coal tars: Implications for risk assessment (ABSTRACT AVAILABLE)
Author(s): Goldstein LS (REPRINT) ; Weyand EH; Safe S; Steinberg M; Culp SJ ; Gaylor DW; Beland FA; Rodriguez LV
Corporate Source: ELECT POWER RES INST,3412 HILLVIEW AVE/PALO ALTO//CA/94303 (REPRINT); RUTGERS STATE UNIV,COLL PHARM/PISCATAWAY//NJ/ ; TEXAS A&M UNIV,DEPT VET PHYSIOL & PHARMACOL/COLLEGE STN//TX/77843; NATL CTR TOXICOL RES,/JEFFERSON//AR/72079; UNIV TEXAS,MD ANDERSON CANCER CTR, DEPT MOL PATHOL/HOUSTON//TX/77030
Journal: ENVIRONMENTAL HEALTH PERSPECTIVES, 1998, V106, 6 (DEC), P1325-1330
ISSN: 0091-6765 Publication date: 19981200
Publisher: US DEPT HEALTH HUMAN SERVICES PUBLIC HEALTH SERVICE, NATL INST HEALTH, NATL INST ENVIRONMENTAL HEALTH SERVICES, PO BOX 12233, RES TRIANGLE PK, NC 27709-2233
Language: English Document Type: ARTICLE
Abstract: Current methods to estimate the quantitative cancer risk of complex mixtures of polycyclic aromatic hydrocarbons (PAH) such as coal tar assume that overall potency can be derived from knowledge of the concentration of a few carcinogenic components such as benzo[a]pyrene (B[a]P). Genotoxic damage, such as DNA adducts, is thought to be an essential aspect of PAH-induced tumorigenesis and could be a biomarker for exposure useful for estimating risk. However, the role of B[a]P and the relationship of adduct formation in tumorigenesis have not been tested rigorously in models appropriate for human health risk assessment. Therefore, we directly compared tumor induction and adduct formation by B[a]P and coal tars in several experimental protocols, including one broadly accepted and used by regulators. We found that B[a]P content did not account for tumor incidences after exposure to coal tars. DNA adducts were found in both rumors and tumor-free tissue and tumor outcomes were not predicted by either quantitation of total DNA adducts or by the DNA adduct formed by B[a]P. These data suggest that risk assessments based on B[a]P content may not predict accurately risk to human health posed by environmental PAH.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

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06979308 Genuine Article#: 110WC Number of References: 7
Title: US Food and Drug Administration perspective of the inclusion of effects of low-level exposures in safety and risk assessment (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT) ; Bolger PM; Schwetz BA
Corporate Source: US FDA,NATL CTR TOXICOL RES, 3900 NCTR RD/JEFFERSON//AR/72079 (REPRINT); US FDA,/ROCKVILLE//MD/20857; US FDA,CTR FOOD SAFETY & APPL NUTR/WASHINGTON//DC/20204
Journal: ENVIRONMENTAL HEALTH PERSPECTIVES, 1998, V106, 1 (FEB), P391-394
ISSN: 0091-6765 Publication date: 19980200
Publisher: US DEPT HEALTH HUMAN SERVICES PUBLIC HEALTH SERVICE, NATL INST HEALTH, NATL INST ENVIRONMENTAL HEALTH SERVICES, PO BOX 12233, RES TRIANGLE PK, NC 27709-2233
Language: English Document Type: ARTICLE
Abstract: A brief overview is provided of some of the general safety and risk assessment procedures used by the different centers of the U.S. Food and Drug Administration (U.S. FDA) to evaluate low-level exposures. The U.S. FDA protects public health by regulating a wide variety of consumer products including foods, human and animal drugs, biologics, and medical devices under the federal Food, Drug, and Cosmetic Act. The diverse legal and regulatory standards in the act allow for the consideration of benefits for some products (e.g., drugs) but preclude them from others (e.g., food additives). When not precluded by statutory mandates (e.g., Delaney prohibition), the U.S. FDA considers both physiologic adaptive responses and beneficial effects. For the basic safety assessment paradigm as presently used, for example in the premarket approval of food additives, the emphasis is on the identification of adverse effects and no observed adverse effect level(s) (NOAEL). Generally, the NOAEL is divided by safety factors to establish an acceptable exposure level. This safely assessment paradigm does not preclude the consideration of effects whether they are biologically adaptive or beneficial at lower dose levels. The flexibility to consider issues such as mechanisms of action and adaptive and beneficial responses depends on the product under consideration. For carcinogenic contaminants and radiation from medical devices, the U.S. FDA considers the potential cancer risk at low exposure levels. This generally involves downward extrapolation from the observed dose-response range. The consideration of adverse effects of other toxicologic end points (e.g., reproductive, immunologic, neurologic, developmental) associated with low exposure levels is also becoming more of a reality (e.g., endocrine disrupters). The evaluation of the biologic effects of low-level exposures to toxic substances must include whether the effect is adverse or a normal physiologic adaptive response and also determine the resiliency of a physiologic system. The public health mandate of the U.S. FDA includes an active research program at the National Center for Toxicological Research and the other U.S. FDA centers to support the regulatory mission of the U.S. FDA. This includes the development of knowledge bases, predictive strategies, and toxicologic studies to investigate effects at the lower end of the dose-response range. Because of the wide diversity of legal and regulatory standards for various products regulated by the U.S. FDA, agency-wide safety and risk assessment procedures and policies generally do not exist.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06979296 Genuine Article#: 110WC Number of References: 51
Title: Upregulation of apoptosis with dietary restriction: Implications for carcinogenesis and aging (ABSTRACT AVAILABLE)

PM3001180942

Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

Author(s): James SJ (REPRINT) ; Muskhelishvili L; Gaylor DW; Turturro A; Hart R
Corporate Source: US FDA,NATL CTR TOXICOL RES, DIV BIOCHEM TOXICOL, 3900 NCTR RD/JEFFERSON//AR/72079 (REPRINT); US FDA,NATL CTR TOXICOL RES, DIV BIOMETRY & RISK ASSESSMENT/JEFFERSON//AR/72079
Journal: ENVIRONMENTAL HEALTH PERSPECTIVES, 1998, V106, 1 (FEB), P307-312
ISSN: 0091-6765 Publication date: 19980200
Publisher: US DEPT HEALTH HUMAN SERVICES PUBLIC HEALTH SERVICE, NATL INST HEALTH, NATL INST ENVIRONMENTAL HEALTH SERVICES, PO BOX 12233, RES TRIANGLE PK, NC 27709-2233
Language: English Document Type: ARTICLE
Abstract: The maintenance of cell number homeostasis in normal tissues reflects a highly regulated balance between the rates of cell proliferation and cell death. Under pathologic conditions such as exposure to cytotoxic, genotoxic, or nongenotoxic agents, an imbalance in these rates may indicate subsequent risk of carcinogenesis. Apoptotic cell death, as opposed to necrotic cell death, provides a protective mechanism by selective elimination of senescent, preneoplastic, or superfluous cells that could negatively affect normal function and/or promote cell transformation. The relative efficiency or dysfunction of the cell death program could therefore have a direct impact on the risk of degenerative or neoplastic disease. Dietary restriction of rodents is a noninvasive intervention that has been reproducibly shown to retard tumor development and most physiologic indices of aging relative to ad libitum-fed animals. As such, it provides a powerful model in which to study common mechanistic processes associated with both aging and cancer. In a recent study we established that chronic dietary restriction (DR) induces an increase in spontaneous apoptotic rate and a decrease in cell proliferation rate in hepatocytes of 12-month-old B6C3F1 DR mice relative to ad libitum (AL)-fed mice. This diet-induced shift in cell death/proliferation rates was associated with a marked reduction in subsequent development of spontaneous hepatoma and a marked increase in disease-free life span in DR relative to AL-fed mice. These results suggest that total caloric intake may modulate the rates of cell death and proliferation in a direction consistent with a cancer-protective effect in DR mice and a cancer-promoting effect in AL mice. To determine whether the increase in spontaneous apoptotic rate was maintained over the life span of DR mice, apoptotic rates were quantified in 12-, 18-, 24- and 30-month-old DR and AL mice. The rate of apoptosis was elevated with age in both diet groups; however, the rate of apoptosis was significantly and consistently higher in DR mice regardless of age. In double-labeling experiments, an age-associated increase in the glutathione S-transferase-II expression in putative preneoplastic hepatocytes in AL mice was rapidly reduced by apoptosis upon initiation of DR. Thus, interventions that promote a low-level increase in apoptotic cell death may be expected to protect genotypic and phenotypic stability with age. If during tumor promotion an adaptive increase in apoptosis effectively balances the dysregulated increase proliferation, the risk of permanent genetic error and carcinogenesis would be minimized.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

06583897 Genuine Article#: ZC636 Number of References: 58
Title: Common mechanism of toxicity: A case study of organophosphorus pesticides (ABSTRACT AVAILABLE)
Author(s): Mileson BE (REPRINT) ; Chambers JE; Chen WL; Dettbarn W; Ehrich M; Eldefrawi AT; Gaylor DW; Hamernik K; Hodgson E; Karczmar AG; Padilla S; Pope CN; Richardson RJ; Saunders DR; Sheets LP; Sultatos LG; Wallace KB
Corporate Source: ILSI RISK SCI INST,/WASHINGTON//DC/20002 (REPRINT);

Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

MISSISSIPPI STATE UNIV,/MISSISSIPPI STATE//MS/39762; DOWELANCO,/INDIANAPOLIS//IN/46206; VANDERBILT UNIV,/NASHVILLE//TN/37240 ; VIRGINIA MARYLAND REG COLL VET MED,/BLACKSBURG//VA/24061; UNIV MARYLAND,SCH MED/COLLEGE PK//MD/20742; US FDA,NATL CTR TOXICOL RES/ROCKVILLE//MD/20857; US EPA,OFF PESTICIDE PROGRAMS/WASHINGTON//DC/20460; N CAROLINA STATE UNIV,/RALEIGH//NC/27695 ; EDWARD HINES JR VET ADM HOSP,/HINES//IL/60141; LOYOLA UNIV,MED CTR/NEW ORLEANS//LA/70118; US EPA,NHEERL/WASHINGTON//DC/20460; NE LOUISIANA UNIV,/MONROE//LA/71209; UNIV MICHIGAN,/ANN ARBOR//MI/48109; TECHNOL SERV GRP,/SILVER SPRING//MD/20910; BAYER CORP,DEPT TOXICOL/PITTSBURGH//PA/15219; UNIV MED & DENT NEW JERSEY,NEW JERSEY MED SCH/NEWARK//NJ/07103; UNIV MINNESOTA,SCH MED/MINNEAPOLIS//MN/55455

Journal: FUNDAMENTAL AND APPLIED TOXICOLOGY, 1998, V41, N1 (JAN), P8-20
ISSN: 0272-0590 Publication date: 19980100
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE

Abstract: The Food Quality Protection Act of 1996 (FQPA) requires the EPA to consider "available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity...in establishing, modifying, leaving in effect, or revoking a tolerance for a pesticide chemical residue." This directive raises a number of scientific questions to be answered before the FQPA can be implemented. Among these questions is: What constitutes a common mechanism of toxicity? The ILSI Risk Science Institute (RSI) convened a group of experts to examine this and other scientific questions using the organophosphorus (OF) pesticides as the case study. OP pesticides share some characteristics attributed to compounds that act by a common mechanism, but produce a variety of clinical signs of toxicity not identical for all OP pesticides. The Working Group generated a testable hypothesis, anticholinesterase OP pesticides act by a common mechanism of toxicity, and generated alternative hypotheses that, if true, would cause rejection of the initial hypothesis and provide criteria for subgrouping OP compounds. Some of the alternate hypotheses were rejected outright and the rest were not supported by adequate data. The Working Group concluded that OP pesticides act by a common mechanism of toxicity if they inhibit acetylcholinesterase by phosphorylation and elicit any spectrum of cholinergic effects. An approach similar to that developed for OP pesticides could be used to determine if other classes or groups of pesticides that share structural and toxicological characteristics act by a common mechanism of toxicity or by distinct mechanisms. (C) 1998 Society of Toxicology.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06468646 Genuine Article#: YV364 Number of References: 51
Title: Health risk assessment practices in the US Food and Drug Administration (ABSTRACT AVAILABLE)
Author(s): Gaylor DW (REPRINT) ; Axelrad JA; Brown RP; Cavagnaro JA; Cyr WH ; Hulebak KL; Lorentzen RJ; Miller MA; Mulligan LT; Schwetz BA
Corporate Source: US FDA,NATL CTR TOXICOL RES/ROCKVILLE//MD/20857 (REPRINT) ; US FDA,CTR DRUG EVALUAT & RES/ROCKVILLE//MD/20857; US FDA,CTR DEVICES & RADIOL HLTH/ROCKVILLE//MD/20857; US FDA,CTR BIOL EVALUAT & RES/ROCKVILLE//MD/20857; US FDA,CTR FOOD SAFETY & APPL NUTR/ROCKVILLE//MD/20857; US FDA,CTR VET MED/ROCKVILLE//MD/20857
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1997, V26, N3 (DEC), P 307-321
ISSN: 0273-2300 Publication date: 19971200
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE

PM3001180944

Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

Abstract: The U.S. Food and Drug Administration (FDA) regulates a wide variety of consumer products. Safety issues involve chemical and microbial contaminants in food, biologics, and medical devices; side effects from prescription and nonprescription drugs; residues of animal drugs in food; and radiation from electronic devices. Because of this wide diversity, the legal standards, rules, and policies governing the regulation of these products differ considerably. Hence, risk assessment and risk management practices within the FDA are of necessity quite diverse. This paper presents a summary of risk assessment practices at each of the product centers of the FDA (Center for Food Safety and Applied Nutrition, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, and Center for Veterinary Medicine) and of the development of risk assessment procedures at the National Center for Toxicological Research. (C) 1997 Academic Press.

Record - 22

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

06465717 Genuine Article#: YV095 Number of References: 26
Title: A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay (ABSTRACT AVAILABLE)
Author(s): Culp SJ (REPRINT) ; Gaylor DW; Sheldon WG; Goldstein LS; Beland FA
Corporate Source: NATL CTR TOXICOL RES,DIV BIOCHEM TOXICOL, HFT-110/JEFFERSON//AR/72079 (REPRINT); PATHOL ASSOCIATES INC,/JEFFERSON//AR/72079; ELECT POWER RES INST,/PALO ALTO//CA/94303
Journal: CARCINOGENESIS, 1998, V19, N1 (JAN), P117-124
ISSN: 0143-3334 Publication date: 19980100
Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD, ENGLAND OX2 6DP
Language: English Document Type: ARTICLE
Abstract: The tumorigenicity of two coal tar mixtures was compared to that of benzo[a]pyrene after 2 years of feeding, Mixture 1, a composite of coal tar from seven coal gasification plant waste sites, was fed to female B6C3F1 mice (48 mice per group) for 2 years at doses of 0.0, 0.01, 0.03, 0.1, 0.3, 0.6 and 1.0%, Mixture 2, which was composed of coal tar from two of the seven waste sites and another site having a high benzo[a]pyrene content, was fed at doses of 0.0, 0.03, 0.1 and 0.3%, Additional groups of mice were fed 0, 5, 25 and 100 ppm benzo[a]pyrene, The coal tar diets induced a dose-related increase in hepatocellular adenomas and carcinomas, alveolar/bronchiolar adenomas and carcinomas, forestomach squamous epithelial papillomas and carcinomas, small intestine adenocarcinomas, histiocytic sarcomas, hemangiosarcomas in multiple organs and sarcomas, Benzo[a]pyrene treatment resulted in an increased incidence of papillomas and/or carcinomas of the forestomach, esophagus and tongue, A comparison of the results indicated that the benzo[a]pyrene in the coal tar diets could be responsible for the forestomach tumors, In contrast, the lung and liver tumors appeared to be due to other genotoxic components contained within the coal tar mixture, while the small intestine tumors resulted from chemically-induced cell proliferation that occurred at high doses of coal tar.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

06205281 Genuine Article#: YB721 Number of References: 29
Title: Some current procedures and issues in cancer risk assessment
Author(s): Gaylor DW (REPRINT)
Corporate Source: US FDA,NATL CTR TOXICOL RES, 3900 NCTR

PM3001180945

Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

RD/JEFFERSON//AR/72079 (REPRINT)
Journal: HUMAN AND ECOLOGICAL RISK ASSESSMENT, 1997, V3, N4 (SEP), P513-519
ISSN: 1080-7039 Publication date: 19970900
Publisher: CRC PRESS INC, 2000 CORPORATE BLVD NW, JOURNALS CUSTOMER SERVICE, BOCA RATON, FL 33431
Language: English Document Type: ARTICLE

Record - 24

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05975113 Genuine Article#: XL600 Number of References: 31
Title: Uncertainty of estimates of cancer risks derived by extrapolation from high to low doses and from animals to humans (ABSTRACT AVAILABLE)
Author(s): Kodell RL (REPRINT) ; Gaylor DW
Corporate Source: US FDA,DIV BIOMETRY & RISK ASSESSMENT, HFT 20, NATL CTR TOXICOL RES, 3900 NCTR RD /JEFFERSON//AR/72079 (REPRINT)
Journal: INTERNATIONAL JOURNAL OF TOXICOLOGY, 1997, V16, N4-5 (JUL-OCT), P 449-460
ISSN: 1091-5818 Publication date: 19970700
Publisher: TAYLOR & FRANCIS LTD, ONE GUNPOWDER SQUARE, LONDON, ENGLAND EC4A 3DE
Language: English Document Type: ARTICLE
Abstract: The uncertainties associated with extrapolating model-based cancer risks from high to low doses and animal-based cancer risks to humans are examined. It is argued that low-dose linear extrapolation based on statistical confidence limits calculated from animal data is designed to account for data uncertainty, model-selection uncertainty, and model-fitting instability. The intent is to err on the side of safety, that is, overstating rather than understating the true risk. The tendency toward conservatism in predicting human cancer risks from animal data based on linear extrapolation is confined by a real-data analysis of the various sources of uncertainty involved in extrapolating from animals to humans. Along with the tendency toward conservatism, a high degree of overall uncertainty in the interspecies extrapolation process is demonstrated. It is concluded that human cancer risk estimates based on animal data may underestimate the true risk by a factor of 10 or may overestimate that risk by a factor of 1,000.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05955236 Genuine Article#: XK161 Number of References: 50
Title: A carcinogenesis model describing mutational events at the DNA adduct level (ABSTRACT AVAILABLE)
Author(s): Zheng Q (REPRINT) ; Lutz WK; Gaylor DW
Corporate Source: NATL CTR TOXICOL RES,DIV BIOMETRY & RISK ASSESSMENT/JEFFERSON//AR/72079 (REPRINT); UNIV WURZBURG,DEPT TOXICOL/D-97078 WURZBURG//GERMANY/
Journal: MATHEMATICAL BIOSCIENCES, 1997, V144, N1 (AUG), P23-44
ISSN: 0025-5564 Publication date: 19970800
Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Abstract: A stochastic carcinogenesis model is proposed to describe a sequence of component mutational changes that constitute the G:C --> A:T base substitution. This paper provides the biological basis and mathematical formulation underlying the proposed model. In addition, the paper elaborates on a numerical approach for studying the cumulant functions, survival functions, and hazard functions of the model.

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Several numerical examples are given of potential applications of the model. (C) 1997 Elsevier Science Inc.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05726709 Genuine Article#: WT986 Number of References: 3
Title: Comments on the EPA uncertainty factor workshop
Author(s): Gaylor DW (REPRINT)
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079 (REPRINT)
Journal: HUMAN AND ECOLOGICAL RISK ASSESSMENT, 1996, V2, N3 (SEP), P405-406
ISSN: 1080-7039 Publication date: 19960900
Publisher: AMHERST SCIENTIFIC PUBL, PO BOX 2308, AMHERST, MA 01004-2308
Language: English Document Type: LETTER

Record - 27

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05543865 Genuine Article#: WF432 Number of References: 19
Title: DNA adduct measurements in relation to small intestine and forestomach tumor incidence during the chronic feeding of coal tar or benzo[a]pyrene to mice (ABSTRACT AVAILABLE)
Author(s): Culp SJ; Gaylor DW; Sheldon WG; Goldstein LS; Beland FA
Corporate Source: NATL CTR TOXICOL RES,/JEFFERSON//AR/72079; PATHOL ASSOCIATES INC,/JEFFERSON//AR/72079; ELECT POWER RES INST,/PALO ALTO//CA/94303
Journal: POLYCYCLIC AROMATIC COMPOUNDS, 1996, V11, N1-4, P161-168
ISSN: 1040-6638 Publication date: 19960000
Publisher: GORDON BREACH SCI PUBL LTD, C/O STBS LTD PO BOX 90, READING, BERKS, ENGLAND RG1 8JL
Language: English Document Type: ARTICLE
Abstract: In a two-year carcinogenicity bioassay, female B6C3F(1) mice were fed up to 100 ppm benzo[a]pyrene (BaP) or up to 1% coal tar in the diet. Forestomach tumors were induced in mice fed BaP, with the incidence increasing sharply between 5 and 25 ppm BaP. Forestomach tumors were also observed in mice fed coal tar, with a pronounced increase at the 0.3% dose. The incidence of forestomach tumors was approximately the same at 0.3% and 0.6% coal tar, but declined at the 1.0% dose, due to early mortality from a high incidence of small intestine adenocarcinomas. DNA adduct levels were examined in the forestomachs and small intestines after feeding BaP or coal tar for 4 weeks.In BaP-treated mice, one major adduct was observed; this adduct accounted for 7-15% of the forestomach adducts in mice fed coal tar. A dose-related increase was observed in adduct levels in the forestomachs of BaP- and coal tar-fed mice. The induction of forestomach tumors from BaP or coal tar was associated with the same levels of BaP-DNA adducts. In the small intestines, total adduct levels increased up to the 0.6% coal tar dose and then decreased at the 1.0% dose. Since the tumor incidence was highest at the 1.0% dose, coal tar-induced cytotoxicity and cell proliferation may be critical factors in tumor induction in this tissue.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05462060 Genuine Article#: WA825 Number of References: 11
Title: QUANTALIZATION OF CONTINUOUS DATA FOR BENCHMARK DOSE ESTIMATION (Abstract Available)

PM3001180947

Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

Author(s): GAYLOR DW
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1996, V24, N3 (DEC), P 246-250
ISSN: 0273-2300
Language: ENGLISH Document Type: ARTICLE
Abstract: Benchmark doses corresponding to low levels of noncancer disease risk have been proposed to replace the no-observed-adverse effect level for establishing allowable daily intakes or reference doses. For quantal data each animal is classified with or without a disease. The proportion of animals with an adverse effect (risk) is observed as a function of dose of a toxic substance. The calculation of a benchmark dose is relatively straightforward. For continuous data a somewhat more complicated designation of risk is required. Because of the more direct procedures with quantal data, consideration could be given to converting continuous data to quantal data before estimating benchmark doses. The purpose of this paper is to compare the precision of the two approaches (use of continuous or quantalized data) for a number of sublinear dose-response curves ranging from low to high probabilities of risk at the highest dose. In these studies, five animals per dose were generally satisfactory to estimate the benchmark dose for continuous data, whereas the corresponding quantalized data generally do not perform as well even with 10 to 20 animals per dose. For quantalized data, the lower 95% confidence limits on the estimates of the benchmark dose were generally a factor of 3 to 4 below the true benchmark dose, whereas the confidence limits using the continuous data were generally within a factor of 2 of the true benchmark dose. Although the use of quantalized data for the estimation of risk is more direct, estimates of benchmark doses using the continuous data were more precise. Based on this study, converting continuous data to quantal data is not recommended. (C) 1996 Academic Press, Inc.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05298784 Genuine Article#: VN670 Number of References: 8
Title: PRECISION OF BENCHMARK DOSE ESTIMATES FOR CONTINUOUS (NONQUANTAL) MEASUREMENTS OF TOXIC EFFECTS (Abstract Available)
Author(s): GAYLOR DW; CHEN JJ
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1996, V24, N1 (AUG), P 19-23
ISSN: 0273-2300
Language: ENGLISH Document Type: ARTICLE
Abstract: The benchmark dose (BMD) corresponding to a low level of the risk of induced disease, e.g., 1 to 10%, has been proposed by various authors as a replacement for the no observed adverse effect level for noncancer endpoints in the regulation of the conditions of exposure to chemicals. This paper focuses on the variability of estimates of the BMD for nonquantal (continuous measurements) of biological endpoints such as are encountered for hematological data, clinical chemistry, and studies of neurotoxic effects. For biological endpoints that can be described by a normal distribution, estimates of the mean and standard deviation are required to calculate the BMD. Estimates of the standard deviation generally are quite variable, particularly for small sample sizes. The purpose of this paper is to examine the precision of the estimates of risk and of the BMD resulting from the inherent variability of the estimates of the standard deviations particularly for bioassays that employ a small number of animals. When the standard deviation is underestimated, the BMD and the regulatory "safe" dose are underestimated. Conversely, when the standard deviation is overestimated, the BMD and safe dose are overestimated. Overestimation

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of the BMD can be reduced or eliminated by using a lower confidence limit. The worst cases arise where only a few animals are used per dose and the dose response is supralinear (changes rapidly at low doses and levels off at higher doses). If the standard deviation is constant across doses (for lognormally distributed data if the coefficient of variation is constant), a pooled estimate across doses of the standard deviation can be used. In this case, for bioassays employing a total of 40 to 50 animals, the calculation of the BMD will generally be within a factor of 2 of the true value. When the standard deviation is not constant across dose groups, it is desirable to have more than 10 animals per dose group. (C) 1996 Academic Press, Inc.

Record - 30

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05095321 Genuine Article#: BE39D Number of References: 18
Title: RISK ASSESSMENT STRATEGIES FOR NEUROPROTECTIVE AGENTS
Author(s): SLIKKER W; GAYLOR DW
Corporate Source: US FDA,NATL CTR TOXICOL RES,DIV NEUROTOXICOL/JEFFERSON//AR/72079; US FDA,NATL CTR TOXICOL RES,DIV BIOMETRY & RISKASSESSMENT/JEFFERSON//AR/72079
Journal: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1995, V765, P198-208
ISSN: 0077-8923
Language: ENGLISH Document Type: ARTICLE

Record - 31

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

04979701 Genuine Article#: UW753 Number of References: 5
Title: THE USE OF UNCERTAINTY FACTORS IN ESTIMATING HEALTH RISKS - REPLY
Author(s): GAYLOR DW; SLIKKER W
Corporate Source: NATL CTR TOXICOL RES,FDA,DIV BIOMETRY & RISK ASSESSMENT/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,FDA,DIV NEUROTOXICOL/JEFFERSON//AR/72079
Journal: FUNDAMENTAL AND APPLIED TOXICOLOGY, 1996, V32, N1 (JUL), P127
ISSN: 0272-0590
Language: ENGLISH Document Type: LETTER

Record - 32

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

04962531 Genuine Article#: UV471 Number of References: 13
Title: ESTIMATING THE PROBABILITY OF OCCURRENCE OF TUMOR FOR A RARE CANCER WITH ZERO OCCURRENCE IN A SAMPLE (Abstract Available)
Author(s): BASU AP; GAYLOR DW; CHEN JJ
Corporate Source: UNIV MISSOURI,DEPT STAT/COLUMBIA//MO/65211; US FDA,NATL CTR TOXICOL RES,DIV BIOMETRY & RISKASSESSMENT/JEFFERSON//AR/72079
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1996, V23, N2 (APR), P 139-144
ISSN: 0273-2300
Language: ENGLISH Document Type: ARTICLE
Abstract: In many physical situations one needs to estimate the probability of occurrence of a rare event based on a random sample when the event has not occurred at all. For example, if the true Lifetime incidence of a tumor at a particular tissue site is less than 1%, it is not uncommon to observe no tumors in a typical sample size of 50 animals. This paper explores the suitability of nonzero Bayesian estimation procedures to replace zero maximum likelihood estimates for tissue sites with nonzero

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background tumor incidences. (C) 1996 Academic Press, Inc.

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(c) 2001 Inst for Sci Info. All rts. reserv.

04920539 Genuine Article#: UR866 Number of References: 12
Title: ON INTERSPECIES CORRELATIONS OF CARCINOGENIC POTENCIES (Abstract Available)
Author(s): KODELL RL; BASU AP; GAYLOR DW
Corporate Source: NATL CTR TOXICOL RES,DIV BIOMETRY & RISK ASSESSMENT,BIOMETRY BRANCH,3900 NCTR RD,HFT-20/JEFFERSON//AR/72079; UNIV MISSOURI,DEPT STAT/COLUMBIA//MO/65211
Journal: JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, 1996, V48, N3 (JUN 28), P231-237
ISSN: 0098-4108
Language: ENGLISH Document Type: ARTICLE
Abstract: It has been established in the literature that constraints on the designs of experiments used to estimate carcinogenic potencies cause overestimation of true biological inter-species correlations of such potencies. This article explores the potential for appreciable underestimation of interspecies correlations, due to the experimental error that occurs in the estimation of carcinogenic potencies.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04802992 Genuine Article#: UJ032 Number of References: 68
Title: RISK-ESTIMATION - AN OVERVIEW - DISEASE RISK-ESTIMATION BASED UPON ANIMAL BIOASSAYS
Author(s): GAYLOR DW
Corporate Source: NATL CTR TOXICOL RES,DIV BIOMETRY & RISK ASSESSMENT,US FDA/JEFFERSON//AR/72079
Journal: DRUG METABOLISM REVIEWS, 1996, V28, N1-2, P9-27
ISSN: 0360-2532
Language: ENGLISH Document Type: ARTICLE

Record - 35

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04730452 Genuine Article#: UD795 Number of References: 17
Title: DOSE-RESPONSE MODELING OF GROWTH FOR DEVELOPMENTAL TOXICITY (Abstract Available)
Author(s): CHEN JJ; GAYLOR DW; LABORDE JB
Corporate Source: US FDA,NATL CTR TOXICOL RES,DIV BIOMETRY & RISKASSESSMENT/JEFFERSON//AR/72079; US FDA,NATL CTR TOXICOL RES,DIV REPROD & DEV TOXICOL/JEFFERSON//AR/72079
Journal: ENVIRONMETRICS, 1996, V7, N2 (MAR-APR), P135-144
ISSN: 1180-4009
Language: ENGLISH Document Type: ARTICLE
Abstract: A biologically-based dose-response model for predicting developmental malformation effects from exposure to a toxic substance during pregnancy is developed. The biological basis of this model arises from the expectation of exponential growth in rodents during gestation, and the exponential growth rate assumed to be reduced by dose raised to a power when a toxic substance is administered during gestation. The prenatal foetal weight is used as a biomarker to link the incidence of cleft palate to the dose level. A dose-response growth model for prenatal foetal weight as a function of both time and dose is

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established. This dose-response function is then combined with a dose-response function between the incidence of cleft palate and the prenatal foetal weight to form a dose-response function between the cleft palate and dose. Two experiments, a dexamethasone (DEX) exposure in rats and a 2,4,5-trichlorophenoxyacetic (2,4,5-T) acid exposure in mice, were conducted for purpose of checking the models empirically and for demonstration of modelling process. The proposed dose-response growth model for prenatal foetal weight fits adequately to both experimental data, but the model from prenatal foetal weight and incidence of cleft palate combined seems inadequate to describe the relationship between the dose and incidence of cleft palate fully.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04238360 Genuine Article#: RQ584 Number of References: 16
Title: QUICK ESTIMATE OF THE REGULATORY VIRTUALLY SAFE DOSE BASED ON THE MAXIMUM TOLERATED DOSE FOR RODENT BIOASSAYS (Abstract Available)
Author(s): GAYLOR DW; GOLD LS
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079; UNIV CALIF BERKELEY/BERKELEY//CA/94720; LAWRENCE BERKELEY LAB/BERKELEY//CA/94720
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1995, V22, N1 (AUG), P 57-63
ISSN: 0273-2300
Language: ENGLISH Document Type: ARTICLE
Abstract: With a limited subset of National Cancer Institute/National Toxicology Program (NCI/NTP) bioassays, Gaylor (Regul. Toxicol. Pharmacol. 9, 101-108, 1989) showed that the regulatory virtually safe dose (VSD), corresponding to an estimated lifetime cancer risk of less than 10(-6), could be estimated within a factor of 10 simply by dividing the maximum tolerated dose (MTD), estimated from the results of a 90-day study, by 380,000. The purpose of this current study was to extend the analysis to all carcinogens in the Carcinogenic Potency Database (CPDB) utilizing the TD50 (average daily dose rate in mg/kg body wt/day that was estimated to halve the probability of remaining tumor-free at a specified tissue site throughout a a-year study). Using the relationship between the upper bound on the low-dose slope (q(1)*) and the TD50 reported by Krewski et al. (Risk. Anal. 13, 383-398, 1993) and the ratio of the maximum dose tested (Max-D)/TD50 obtained in our present analysis, an estimate of the regulatory VSD was given by the MTD/740,000, for NCI/NTP rodent carcinogens. This was about a factor of two lower than the limited analysis conducted by Gaylor. There was little difference when the chemicals were divided into mutagens and nonmutagens. Ninety-six percent (134 of the 139 NCI/NTP rodent carcinogens) of the regulatory VSDs calculated from the individual TD(50)s obtained from the 2-year bioassays were within a factor of 10 of the MTD/740,000. Gold et al. (Environ. Health Perspect. 79, 259-272, 1989) investigated the distribution of the TD50 among "near-replicate" experiments (where the same chemical was tested more than once and was positive in the same strain, sex, and species by the same route). The distribution of TD(50)s from near-replicate experiments is similar to the distribution of the Max-D/TD50. Hence, the estimate of the regulatory VSD based on the Max-D/740,000, for NCI/NTP bioassays, is about as precise as the estimate obtained from a 2-year bioassay. This questions the advisability of conducting a 2-year bioassay for purposes of regulatory risk estimation. Since resources are available to test only a small fraction of chemicals to which humans are exposed, a preliminary estimate of the regulatory VSD can be useful in setting testing priorities. If the expected human exposure level is below the regulatory VSD estimated from the MTD, a chemical may be assigned low priority for testing in a 2-year bioassay. Based on

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previous work the FDA proposed a "threshold of regulation" of a dietary concentration of 0.5 ppb for all substances used in food-contact articles. The results of the present analysis could be used to make the procedure more chemical specific based upon an available MTD. The high correlation between the MTD and estimate of cancer potency (TD50) can be exploited to provide a preliminary, hypothetical upper bound estimate of cancer risk for exposure to a chemical without conducting a 2-year animal bioassay. Thus, the expected level of human exposure relative to the MTD can be used to determine the priority for further research on a chemical, such as mechanistic studies. (C) 1995 Academic Press, Inc.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04238355 Genuine Article#: RQ584 Number of References: 10
Title: NEUROTOXICITY MODELING FOR RISK ASSESSMENT (Abstract Available)
Author(s): KODELL RL; CHEN JJ; GAYLOR DW
Corporate Source: US FDA,NATL CTR TOXICOL RES,DIV BIOMETRY & RISKASSESSMENT/JEFFERSON//AR/72079
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1995, V22, N1 (AUG), P 24-29
ISSN: 0273-2300
Language: ENGLISH Document Type: ARTICLE
Abstract: The setting of acceptable exposure levels for neurotoxicants has followed the traditional approach of dividing experimental no-observed-adverse-effect-levels (NOAELs) by safety/uncertainty factors. NOAELs are believed by many toxicologists to represent levels having zero or negligible risk, while uncertainty factors are used to account for a number of sources of variation. Although the use of NOAELs in this manner has been criticized because of their imprecise quantitative definition, NOAELs for nonquantal neurotoxic effects have not been replaced by more precisely defined quantities (e.g., benchmark doses), partly due to the absence of a generally accepted methodology for attaching specific risk levels to low exposures. The present paper describes a quantitative approach to modeling nonquantal neurotoxic effects for risk assessment, which can be used to obtain results similar to the familiar results obtained in risk assessment for carcinogenicity and developmental toxicity. The steps involved in implementing the process are discussed, with particular attention being given to the critical step of defining an adverse neurologic effect. An experimental data set is used to illustrate the methodology. (C) 1995 Academic Press, Inc.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04147912 Genuine Article#: RH947 Number of References: 22
Title: SPONTANEOUS RENAL TUBULAR CARCINOMA IN FISCBER-344 RAT LITTERMATES (Abstract Available)
Author(s): THURMAN JD; HAILEY JR; TURTURRO A; GAYLOR DW
Corporate Source: SPRINGBORN LABS,640 W ELIZABETH ST/SPENCERVILLE//OH/45887
Journal: VETERINARY PATHOLOGY, 1995, V32, N4 (JUL), P419-422
ISSN: 0300-9858
Language: ENGLISH Document Type: NOTE
Abstract: Two of 632 Fischer-344 rats in a food restriction study had spontaneous, bilateral, multicentric renal tubular cell carcinomas. Although there were 104 litters represented in this study, both rats that developed this rare neoplasm were from the same litter. The littermates, one male and one female, were in the food-restricted

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treatment groups (60% of ad libitum intake) and were 550 and 447 days old, respectively, at death. The probability that the two rare bilateral renal neoplasms occurred by a chance event in littermates is approximately 0.8%. The apparent familial predisposition for development of specific types of neoplasms emphasizes the importance of randomization of individuals into treatment groups and consideration of lineage for rare tumors.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04051807 Genuine Article#: QL060 Number of References: 20
Title: LIMITATIONS OF PROBIT PLOTS IN PHARMACOGENETICS - REQUIREMENT OF GENETIC ANALYSES TO TEST HYPOTHESES BASED ON GRAPHICAL METHODS
Author(s): VESELL ES; GAYLOR DW
Corporate Source: PENN STATE UNIV,COLL MED,DEPT PHARMACOL,POB 850/HERSHEY//PA/17033; US FDA,PUBL HLTH SERV,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: PHARMACOGENETICS, 1995, V5, N1 (FEB), P18-23
ISSN: 0960-314X
Language: ENGLISH Document Type: EDITORIAL

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03122838 Genuine Article#: NG419 Number of References: 24
Title: STUDY OF SODIUM SACCHARIN CO-CARCINOGENICITY IN THE RAT (Abstract Available)
Author(s): WEST RW; SHELDON WG; GAYLOR DW; ALLEN RR; KADLUBAR FF
Corporate Source: NATL CTR TOXICOL RES,DIV BIOCHEM TOXICOL/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,PATHOL ASSOCIATES INC/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,BIOMETRY STAFF/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,COMP BASED SYST INC/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,RES OFF/JEFFERSON//AR/72079
Journal: FOOD AND CHEMICAL TOXICOLOGY, 1994, V32, N3 (MAR), P207-213
ISSN: 0278-6915
Language: ENGLISH Document Type: ARTICLE
Abstract: A co-carcinogenicity experiment was conducted with female Sprague-Dawley rats in which the effects of short-term sodium saccharin dosing and initiation with a direct-acting carcinogen were examined in the urinary bladder. All initiated animals were administered 0.5 mg N-methyl-N-nitrosourea (MNU) by instillation into the bladder at 8 wk of age. The animals were also given saccharin at one of four levels in the diet (0, 1.0, 2.5 or 5%) for 4 wk either (1) just before treatment with MNU (4-8 wk of age), (2) centred on treatment with MNU (6-10 wk of age) or (3) after MNU treatment (8-12 wk of age). Additionally, a group of animals was exposed to saccharin through the milk for 3 wk by dosing the mothers, starting on the day of parturition. The animals were held on control diet until interim killing of 20 animals per group at about 590 days of age, removal for morbidity, or terminal killing of the remainder of 60 animals per treatment around 780 days of age. A histopathological examination was made of the urinary tract and the relationship of saccharin dose to bladder tumour prevalence analysed statistically. A consistent increase (with very weak statistical significance) in tumour rate at interim killing, and for the pathology data overall, was shown by the 2.5% dose group given saccharin from 8 to 12 wk of age. Tumour prevalences of 47.6 and 40.7% v. control prevalences of 21.1 and 25.4% were observed for the two time periods (P values <0.076 and <0.0853, respectively). All groups given saccharin

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neonatally showed increased tumour prevalence for both time periods, but none of the differences was statistically significant at the 95% confidence level. No consistent increase in tumour prevalence was seen in the groups given saccharin from 4 to 8 or 6 to 10 wk of age; thus, these data suggest that saccharin does not act as a strong cocarcinogen in the MNU-treated rat bladder.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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02717605 Genuine Article#: LZ143 Number of References: 15
Title: SUBCHRONIC STUDIES OF PYRILAMINE IN B6C3F(1) MICE (Abstract Available)
Author(s): GREENMAN DL; MORRISSEY R; GAYLOR DW; ALLABEN WT
Corporate Source: NATL CTR TOXICOL RES,OFF SCI COORDINAT/JEFFERSON//AR/72079; PATHOL ASSOCIATES INC/JEFFERSON//AR/00000
Journal: JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY, 1993, V12, N4 (AUG) , P337-345
ISSN: 0730-0913
Language: ENGLISH Document Type: ARTICLE
Abstract: The purpose of this study was to determine the effects of subchronic exposure to the antihistamine pyrilamine maleate and to establish dosage levels to use in a 2-year chronic study. A 14-day repeated-dose study in male and female B6C3F1 mice at dietary levels of pyrilamine (as the free base) of 0, 196, 392, 783, 1563, or 3122 ppm revealed no influence on body weight gain and resulted in no deaths, nor abnormal clinical or gross necropsy observations. Parotid gland cell necrosis was more apparent in high-dosage groups than in controls of either gender. Male and female B6C3F1 mice also were administered pyrilamine for 90 days at dietary concentrations of 0, 375, 750, 1500, 3000, or 6000 ppm. Weight gain was markedly suppressed in the 6000 ppm group, but less so at 1500 and 3000 ppm. Parotid gland cell necrosis was apparent in males receiving 750 ppm pyrilamine and above and in females at 1500 ppm and above. Cytomegaly was noted in the parotid glands of both sexes at midlevel dosages but not in control, low-dosage, or high-dosage animals. It was concluded that 1500 ppm pyrilamine would not be life-threatening to B6C3F1 mice in a chronic study.

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02458217 Genuine Article#: LC608 Number of References: 17
Title: SUBCHRONIC STUDIES OF PYRILAMINE IN FISCHER 344 RATS (Abstract Available)
Author(s): GREENMAN DL; MORRISSEY R; GAYLOR DW; ALLABEN WT
Corporate Source: NATL CTR TOXICOL RES,OFF SCI COORDINAT/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,PATHOL ASSOCIATES INC/JEFFERSON//AR/72079
Journal: JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY, 1993, V12, N2 (APR) , P175-183
ISSN: 0730-0913
Language: ENGLISH Document Type: ARTICLE
Abstract: This study was designed to determine the subchronic effects of the antihistamine, pyrilamine maleate, and to establish dose levels for a 2-year chronic study. Six male and six female F344 rats received dietary pyrilamine concentrations of 0, 392, 783, 1563, 3122, or 6276 ppm (as the free base) for 14 days. Only weight gain suppression was noted, at 3122 and 6276 ppm, especially in males. When 12 male and 12

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female F344 rats were fed pyrilamine for 90 days at 0, 750, 1500, 3000, 6000, or 12,000 ppm, weight gain was suppressed and organ/body weight ratios often were higher than in controls at 3000 ppm and above. Heart/brain and thymus/brain ratios were decreased at 3000 ppm and above in males and at 6000 or 12,000 ppm in females. All rats receiving 6000 or 12,000 ppm pyrilamine exhibited severe diffuse parenchymal cell cytomegaly in the parotid salivary glands with a dose-related decrease in severity and prevalence at lower concentrations. Hepatocellular vacuolization, present only in males, increased in severity with dose, starting at 750 ppm. The severity of liver fatty metamorphosis increased with dose at the three low doses but was less apparent and/or disappeared at 6000 and 12,000 ppm. It was concluded that 3000 ppm pyrilamine would not be life threatening to F344 rats in a chronic study.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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02364517 Genuine Article#: KW876 Number of References: 31
Title: DOSE-RESPONSE MODELS FOR DEVELOPMENTAL MALFORMATIONS (Abstract Available)
Author(s): GAYLOR DW; CHEN JJ
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: TERATOLOGY, 1993, V47, N4 (APR), P291-297
ISSN: 0040-3709
Language: ENGLISH Document Type: ARTICLE
Abstract: An empirical dose-response model can generally be found for bioassay data, which provides a mathematical relationship between the incidence of a developmental malformation and dose of a toxicant in the experimental dose range. If biological principles and data can be used in the formulation of the dose-response model, the estimation of the incidence of malformations outside of the experimental dose range may be improved. In this paper, exponential growth of morphological structures in rodents during gestation is assumed. Further, it is assumed that some structural malformations are the result of reduced or delayed growth and the incidence of structurally normal fetuses is proportional to fetal weight raised to a power. When the exponential growth rate constant is reduced by dose raised to a power, a Weibull dose-response function is obtained. When the exponential growth rate constant is modeled by a polynomial function of dose, a polynomial-exponential dose-response model is obtained. The Weibull and the polynomial-exponential model, restricted to degrees from one up to the number of dosed groups, were fit to a database of bioassay data assembled from Teratology Vol. 1 (1968) to Vol. 42 (1990). In general the two models gave similar results and often gave exactly the same fit. The linear term appeared in the polynomial-exponential model in about one-fourth of the cases and was not related to the background incidence.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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02173843 Genuine Article#: KG637 Number of References: 10
Title: APPLICATION OF BIOMARKERS TO RISK ASSESSMENT (Abstract Available)
Author(s): GAYLOR DW; KADLUBAR FF; BELAND FA
Corporate Source: US FDA,NATL CTR TOXICOL RES,BIOMETRY STAFF/JEFFERSON//AR/72079
Journal: ENVIRONMENTAL HEALTH PERSPECTIVES, 1992, V98, NOV (NOV), P139-141
ISSN: 0091-6765
Language: ENGLISH Document Type: ARTICLE

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Source: https://www.industrydocuments.ucsf.edu/docs/ykfk0001

Abstract: Due to difficulties in conducting epidemiological studies, most estimates of cancer risk are based on data from animal bioassays. Extrapolation of cancer risk estimates in animals to humans requires an assumption of equal potency across species based on the average daily dose. The purpose of this paper is to examine the ability to predict tumor incidence across species from DNA adduct concentrations resulting from exposure to carcinogens. A 100-fold range of structurally diverse adduct concentrations corresponding to the same tumor incidence raises questions about quantitative predictability across chemical classes and across species. Differences in adduct structure, mutagenic efficiency, adduct repair rates, and cellular proliferation could account for some of the differences. For specific carcinogen-DNA adducts, the steady-state levels associated with a 50% tumor incidence appear to vary over a narrower range. An equal incidence of liver tumors was obtained at equal concentrations of aflatoxin B1-DNA adducts for rats and trout. A 2- to 3-fold range of 4-aminobiphenyl-DNA adduct concentrations between mice and dogs appears to be associated with nearly equal bladder tumor incidence, on the basis of limited data. In humans, a 5-fold higher concentration of a 4-aminobiphenyl-DNA adduct in bladders of smokers than of nonsmokers is compatible with the relative risk of bladder cancer due to smoking. DNA adduct concentrations certainly can be used to improve quantification of chemical exposures for epidemiological studies. Although promising, more data are needed to judge the usefulness of DNA adduct concentrations to predict cancer incidence across species.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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02137843 Genuine Article#: KE112 Number of References: 7
Title: PROCESS OF BUILDING BIOLOGICALLY BASED DOSE-RESPONSE MODELS FOR DEVELOPMENTAL DEFECTS (Abstract Available)
Author(s): GAYLOR DW; RAZZAGHI M
Corporate Source: US FDA,NATL CTR TOXICOL RES,BIOMETRY STAFF,HFT-20/JEFFERSON//AR/72079; BLOOMSBURG UNIV/BLOOMSBURG//PA/17815
Journal: TERATOLOGY, 1992, V46, N6 (DEC), P573-581
ISSN: 0040-3709
Language: ENGLISH Document Type: ARTICLE
Abstract: The problem of developing biologically-based dose-response models is addressed for predicting the prevalence of birth defects at low doses of toxic chemicals administered during pregnancy. To illustrate the process of incorporating biological information, a model is postulated to predict the prevalence of cleft palate for a chemical that reduces embryonic/fetal growth, which results in inadequate palatal cells for closure. Experimental bioassay data examining the prevalence of cleft palate in mice exposed to the herbicide 2,4,5-T are used to illustrate the process. With the limited data available, it is necessary to assume a model for cell growth and the relationship between the cell growth rate parameter and dose of 2,4,5-T. Also, a relationship between cleft palate prevalence and growth is assumed and then checked with experimental data. The purpose of the paper is not to provide a universal biologically based dose-response model for cleft palate, but rather to demonstrate the extent, and type of information and data required. It remains to be seen if the form of the model is appropriate for chemicals that primarily produce embryo/fetal malformations or death via reduced or delayed cellular growth.

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02129532 Genuine Article#: KD322 Number of References: 76
Title: AN INVITRO PANCREAS ACINAR CELL MODEL FOR TESTING THE MODULATING EFFECTS OF CALORIC RESTRICTION AND AGING ON CELLULAR PROLIFERATION AND TRANSFORMATION (Abstract Available)
Author(s): HASS BS; HART RW; GAYLOR DW; POIRIER LA; LYNCOOK BD
Corporate Source: US FDA,DEPT HLTH & HUMAN SERV,NATL CTR TOXICOL RES,DIV NUTR TOXICOL/JEFFERSON//AR/72079; US FDA,DEPT HLTH & HUMAN SERV,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: CARCINOGENESIS, 1992, V13, N12 (DEC), P2419-2425
ISSN: 0143-3334
Language: ENGLISH Document Type: ARTICLE
Abstract: Pancreatic acinar cells were isolated for culture from a young (Y) and an old (O) Brown-Norway or Fischer 344 rat fed an ad libitum (AL) or calorically restricted (CR) diet. The cells were cultured and cellular growth rates were determined as a function of passage number. An overall increase in cellular growth rate and transformation frequency with age and/or AL diet relative to youth as well as a decrease with CR diet were concordant with reported responses in vivo. Transformation frequency was measured in Brown-Norway cells and followed the same pattern as the growth response: AL/O > AL/Y = CR/Y > CR/O. The cellular model is shown to fit the general multistage requirements of the carcinogenic process as well as general age and diet characteristics of pancreatic cancer. This pancreatic acinar cell age-diet approach may prove to be a valuable tool for determining mechanisms of exocrine pancreatic carcinogenesis as well as other disease states; it may also be of utility in in vitro gerontological nutritional and pharmacological studies since some of the age and diet determinants of biological effects appear to be segregable. Propensity of cells from an old and/or AL diet animal for faster growth and for cellular transformation are programmed into the cells by the time of their excision from the animal (as late as 14 months), indicating a heritable component in the model or a mechanism that is dependent upon elements that control gene expression.

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01865245 Genuine Article#: JG896 Number of References: 25
Title: DEVELOPMENTAL TOXICITY OF 2,4,5-TRICHLOROPHENOXYACETIC ACID (2,4,5-T) .1. MULTIREPLICATED DOSE-RESPONSE STUDIES IN 4 INBRED STRAINS AND ONE OUTBRED STOCK OF MICE
Author(s): HOLSON JF; GAINES TB; NELSON CJ; LABORDE JB; GAYLOR DW; SHEEHAN DM; YOUNG JF
Corporate Source: WIL RES LABS INC/ASHLAND//OH/44805; US EPA MD-56/RES TRIANGLE PK//NC/27711; NATL CTR TOXICOL RES,FOOD & DRUG ADM,DEPT HLTH & HUMAN SERV,DIV REPROD & DEV TOXICOL/JEFFERSON//AR/72079
Journal: FUNDAMENTAL AND APPLIED TOXICOLOGY, 1992, V19, N2 (AUG), P286-297
Language: ENGLISH Document Type: ARTICLE

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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01857048 Genuine Article#: JG591 Number of References: 6
Title: RELATIONSHIP BETWEEN THE SHAPE OF DOSE-RESPONSE CURVES AND BACKGROUND TUMOR RATES
Author(s): GAYLOR DW
Corporate Source: NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1992, V16, N1 (AUG), P2-9
Language: ENGLISH Document Type: ARTICLE

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01855782 Genuine Article#: JF876 Number of References: 10
Title: DOSE-RESPONSE MODELING OF QUANTITATIVE RESPONSE DATA FOR RISK ASSESSMENT (Abstract Available)
Author(s): CHEN JJ; GAYLOR DW
Corporate Source: US FDA,NAT CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: COMMUNICATIONS IN STATISTICS-THEORY AND METHODS, 1992, V21, N8, P 2367-2381
Language: ENGLISH Document Type: ARTICLE
Abstract: The current regulation of non-carcinogenic effects has generally been based on dividing a safety factor into an experimental no-observed-effect-level (NOEL), giving a regulatory reference dose (RfD). This approach does not attempt to estimate the risk as a function of dose; it assumes no significant risk for the dose below the RfD. This paper proposes a mathematical model for finding the upper confidence limit on risk and lower confidence limit on dose for quantitative risk assessment when the responses follow a normal distribution. The proposed procedure appears to be conservative; this is supported by results of a simulation study. The procedure is illustrated by application to real data.

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01844158 Genuine Article#: JF196 Number of References: 19
Title: INTERNATIONAL TRENDS IN THE INCIDENCE OF BONE CANCER ARE NOT RELATED TO DRINKING-WATER FLUORIDATION (Abstract Available)
Author(s): FRENI SC; GAYLOR DW
Corporate Source: US FDA,NATL CTR TOXICOL RES,DIV BIOMETRY & RISKASSESSMENT/JEFFERSON//AR/72079
Journal: CANCER, 1992, V70, N3 (AUG 1), P611-618
Language: ENGLISH Document Type: ARTICLE
Abstract: Background. Because osteosarcomas may develop in rats exposed to fluoridated water, water fluoridation might pose a cancer risk to humans.

Methods. A time trend analysis of the cumulative risk (CR) of bone cancer for the period 1958-1987 for 40 cancer registry areas showed an increased risk for young males in Canada, Europe, and the United States, and a decreased lifetime risk for either sex in Europe.

Results. This was unrelated to water fluoridation and may have resulted from changes in coding practices. Bone cancer risk was inversely related to the incidence of cancers of unknown origin, suggesting that bone metastases were erroneously coded as primary bone cancer. In 1968-1972, most areas recorded more bone cancer deaths than new cases of the disease.

Conclusions. The mortality/incidence ratio, but not the incidence rate (IR), has dropped sharply since then, which erodes the basis of past inferences relating cancer mortality to fluoridation.

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01694196 Genuine Article#: HT560 Number of References: 6

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Title: INCIDENCE OF DEVELOPMENTAL DEFECTS AT THE NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL)
Author(s): GAYLOR DW
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: REGULATORY TOXICOLOGY AND PHARMACOLOGY, 1992, V15, N2 (APR), P 151-160
Language: ENGLISH Document Type: ARTICLE

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01529392 Genuine Article#: HF961 Number of References: 15
Title: CORRELATIONS OF DEVELOPMENTAL END-POINTS OBSERVED AFTER 2,4,5-TRICHLOROPHENOXYACETIC ACID EXPOSURE IN MICE (Abstract Available)
Author(s): CHEN JJ; GAYLOR DW
Corporate Source: US FDA,NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: TERATOLOGY, 1992, V45, N3 (MAR), P241-246
Language: ENGLISH Document Type: ARTICLE
Abstract: A large-scale developmental toxicology study of 2,4,5-trichlorophenoxyacetic acid was conducted in four inbred strains and one outbred strain of mice. The most significant developmental effects observed were reduced fetal weight and increased incidences of cleft palate (malformation) and prenatal death (deaths/resorptions). The correlation coefficients among the proportion of deaths/resorptions, proportion of malformations, average fetal weights, and number of viable fetuses were investigated, with each variable measured on a per-litter basis. Generally, the correlation coefficients between average fetal weight and number of viable fetuses were negative for the control and low-dose groups in the C57BL/6, C3H/He, and BALB/c strains. Overall, the correlation coefficients between proportion of malformations and number of viable fetuses were not significant. The correlation coefficients between proportion of malformations and average fetal weight were negative for all but one case. The correlations were weak in the control and low-dose groups, in which the malformation rates were very low, and were strong in the high-dose groups. The correlation coefficients between proportion of deaths/resorptions and proportion of malformations were generally positive at the high doses; some negative correlations were observed in control and low-dose groups. The correlation coefficients between proportion of deaths/resorptions and average fetal weight were negative for the A/JAX and CD-1 strains. In summary, the strongest relationship observed was the negative correlation between fetal weight and malformation.

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01235383 Genuine Article#: GG509 Number of References: 7
Title: ANALYSIS OF TRINOMIAL RESPONSES FROM REPRODUCTIVE AND DEVELOPMENTAL TOXICITY EXPERIMENTS (Abstract Available)
Author(s): CHEN JJ; KODELL RL; HOWE RB; GAYLOR DW
Corporate Source: NATL CTR TOXICOL RES,FOOD & DRUG ADM,BIOMETRY STAFF/JEFFERSON//AR/72079
Journal: BIOMETRICS, 1991, V47, N3, P1049-1058
Language: ENGLISH Document Type: ARTICLE
Abstract: This paper presents a Dirichlet-trinomial distribution for modelling data obtained from reproductive and developmental studies. The common endpoints for the evaluation of reproductive and developmental toxic effects are the number of dead fetuses, the number

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of malformed fetuses, and the number of normal fetuses for each litter. With current statistical methods for the evaluation of reproductive and developmental effects, the effect on the number of deaths and the effect on the number of malformations are analyzed separately. The Dirichlet-trinomial model provides a procedure for the analysis of multiple endpoints simultaneously. This proposed Dirichlet-trinomial model is a generalization of the beta-binomial model that has been used for handling the litter effect in reproductive and developmental experiments. Likelihood ratio tests for differences in the number of deaths, the number of malformations, and the number of normals among dosed and control groups are derived. The proposed test procedure based on the Dirichlet-trinomial model is compared with that based on the beta-binomial model with an application to a real data set.

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01122479 Genuine Article#: FY148 Number of References: 31
Title: BLADDER AND LIVER TUMORIGENESIS INDUCED BY 2-ACETYLAMINOFLUORENE IN DIFFERENT-F1 MOUSE HYBRIDS - VARIATION WITHIN GENOTYPES AND EFFECTS OF USING MORE THAN ONE GENOTYPE ON RISK ASSESSMENT (Abstract Available)
Author(s): WOLFF GL; GAYLOR DW; BLACKWELL BN; MOORE GE
Corporate Source: US FDA,NATL CTR TOXICOL RES,DIV COMPARAT TOXICOL/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,PATHOL ASSOCIATES INC/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,COMP BASED SYST INC/JEFFERSON//AR/72079
Journal: JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, 1991, V33, N3, P 327-348
Language: ENGLISH Document Type: ARTICLE
Abstract: Several F1 mouse hybrids were used in a chronic bioassay to determine whether such an experimental design would provide greater statistical power than using only the B6C3F1 hybrid. For this purpose, the dose response of formation of hepatocellular and bladder tumors after 30 mo of feeding 2-acetylaminofluorene (2-AAF) in the diet was assessed in 4 F1 mouse hybrids, including the B6C3F1 hybrid. No strain background-related differences in frequency of bladder neoplasms between any F1 hybrids were detected. Bladder tumors occurred only at the highest 2-AAF dose in female mice. In males the lowest dose was already sufficient to induce bladder neoplasms with incidences of 25-48% adjusted for different nontumor mortality patterns across doses. No marked strain-related differences in hepatocellular tumor rates were apparent in either sex. Higher frequencies of hepatocellular neoplasms were observed among the untreated control males of the B6C3, AY, and CVA F1 hybrids than among the comparable females. Among treated mice, the lowest 2-AAF dose increased liver tumor incidence, more so among the females than among the males. The different background genomes resulted in somewhat different risk assessments for liver tumor formation in males due to differences in the time-to-tumor curves.

Except for the much higher background liver tumor rate in the CVY mice, the adjusted liver tumor incidences were similar across the four hybrids. Hence, the levels of statistical significance obtained for dose-response trends and comparisons of treated and control groups were similar using 48 animals per dose group with B6C3 mice, or combinations of 24 animals per dose from 2 genotypes, or 12 animals per dose from the 4 hybrid genotypes. Estimates of carcinogenic potency for bladder tumors were similar, within a factor of two, across the four hybrids. However, estimates of liver tumor potency across genotypes varied by a factor of two and six for females and males, respectively. Thus, the mean of cancer potency estimates across these genotypes would be more representative for mice than results from any single genotype.

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As in chronic carcinogenesis studies with other test agents, neoplasms developed in only a certain proportion, rather than in all, of the genetically identical animals exposed to a given dose of the toxicant for the same length of time under the same controlled environmental conditions. This phenotypic variability in toxic responses may reflect differential regulation of gene expression among the genetically identical test animals.

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00761948 Genuine Article#: EU614 Number of References: 11
Title: CARCINOGENIC POTENCY CORRELATIONS - REAL OR ARTIFACTUAL
Author(s): KODELL RL; GAYLOR DW; CHEN JJ
Corporate Source: US FDA,NATL CTR TOXICOL RES,BIOMETRY STAFF,HFT-20/JEFFERSON//AR/72079
Journal: JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH, 1991, V32, N1, P 1-9
Language: ENGLISH Document Type: ARTICLE

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00465197 Genuine Article#: DU928 Number of References: 8
Title: RISK ASSESSMENT FOR NEUROTOXIC EFFECTS
Author(s): GAYLOR DW; SLIKKER W
Corporate Source: NATL CTR TOXICOL RES,HFT-20/JEFFERSON//AR/72079
Journal: NEUROTOXICOLOGY, 1990, V11, N2, P211-218
Language: ENGLISH Document Type: ARTICLE

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00341476 Genuine Article#: DJ591 Number of References: 3
Title: BEHAVIORAL TERATOGENIC EFFECT OF METHYLMERCURY AND D-AMPHETAMINE - METAANALYSIS AND POWER ANALYSIS OF DATA FROM THE COLLABORATIVE BEHAVIORAL TERATOLOGY STUDY OF NATIONAL-CENTER-FOR-TOXICOLOGICAL-RESEARCH - COMMENTS
Author(s): GAYLOR DW
Corporate Source: NATL CTR TOXICOL RES/JEFFERSON//AR/72079
Journal: TERATOLOGY, 1990, V41, N6, P749-750
Language: ENGLISH Document Type: LETTER

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00294454 Genuine Article#: DE389 Number of References: 20
Title: CHRONIC TOXICITY CARCINOGENICITY STUDIES OF SULFAMETHAZINE IN FISCHER 344/N RATS - 2-GENERATION EXPOSURE
Author(s): LITTLEFIELD NA; SHELDON WG; ALLEN R; GAYLOR DW
Corporate Source: US FDA,NATL CTR TOXICOL RES,DEPT HLTH & HUMAN SERV/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,COMP BASED SYST INC/JEFFERSON//AR/72079; NATL CTR TOXICOL RES,PATHOL ASSOCIATES INC/JEFFERSON//AR/72079
Journal: FOOD AND CHEMICAL TOXICOLOGY, 1990, V28, N3, P157-167
Language: ENGLISH Document Type: ARTICLE

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